UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/990,574	11/21/2001	Pravin T.P. Kaumaya	18525/04028	2019

24024 7590 12/15/2004

CALFEE HALTER & GRISWOLD, LLP
800 SUPERIOR AVENUE
SUITE 1400
CLEVELAND, OH 44114

EXAMINER	
OUSPENSKI, ILIA I	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 12/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/990,574	KAUMAYA ET AL.	
	Examiner	Art Unit	
	ILIA OUSPENSKI	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *9,11,12 and 17-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10 and 13-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03/24/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1 – 32 are pending.

2. Applicant's election with traverse of Group I, claims 1 – 16, drawn to a CD28 peptide mimetic for blocking deleterious T cell mediated immune reactions, in the reply filed on 10/14/2004 is acknowledged. Applicant further elects the species wherein the peptide mimetic comprises SEQ ID NO:5.

The traversal is on the ground(s) that consideration of Inventions of Groups I and II would not result in a serious burden on the Office. This is not found persuasive because, as pointed out in the Restriction Requirement, a prior art search also includes a literature search. It is and undue burden to for the examiner to search more than one invention.

The requirement is still deemed proper and is therefore made FINAL.

Upon further consideration, the prior art search has been extended to include the species wherein the peptide mimetic comprises SEQ ID NOS:1, 2, 3, and 6.

Claims 17 – 32 (non-elected group II) and claims 9, 11, and 12 (non-elected species of elected group I) are withdrawn from further consideration by the Examiner, under 37 C.F.R. § 1.142(b), as being drawn to nonelected inventions.

Claims 1 – 8, 10, and 13 – 16 are under consideration in the instant application.

3. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth herein.

Upon review of the instant application, it is noted that the sequences disclosed at least in the Abstract and on page 3 *are not accompanied by SEQ ID Numbers.* Applicant is reminded of the sequence rules which require a submission for all sequences of more than 9 nucleotides or 3 amino acids (see 37 CFR 1.821-1.825) and is also requested to carefully review the submitted specification for any and all sequences which require compliance with the rules.

Furthermore, the proper format of sequence identifier is "SEQ ID NO:X", wherein the "NO" and the number are separated by a colon. See MPEP §2422.

Applicant is reminded to amend the specification and the claims accordingly.

Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) in response to this Office Action.

4. In view of the papers filed 10/07/2002, it has been found that this nonprovisional application, as filed, through error and without deceptive intent, improperly set forth the inventorship, and accordingly, this application has been corrected in compliance with 37 CFR 1.48(a). The inventorship of this application has been changed to add Mythily Srinivasan as named inventor to the instant application.

5. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. The provisional applications USSN 60/252,744 and 60/250,984 upon which priority is claimed appears to provide adequate support under 35 U.S.C. 112 for peptide mimetics of SEQ ID NOS:1 – 8.

However, the provisional applications upon which priority is claimed fail to provide sufficient support under 35 U.S.C. 112 for the claimed subject matter of peptide mimetics of SEQ ID NOS:9 – 10.

Consequently, the instant claims 12 – 16 have been accorded the priority of the filing date of the instant application, i.e. 11/21/2001.

Should Applicant disagree with the Examiner's factual determination above, it is incumbent upon Applicant to provide a showing that specifically supports the instant claim limitations.

6. Applicant is reminded of the proper language and format for an Abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

In the instant case, the abstract exceeds 150 words, and the use of the word "hereinafter" is improper.

Furthermore, the abstract of the disclosure is objected to because of apparent spelling errors, such as "peptides ," (line 2), lacking period at the end of the sentence (line 12), and an apparently superfluous numeral at line 14. Correction is required. See MPEP § 608.01(b).

7. Applicant's IDS, filed 03/24/2003, is acknowledged, and has been considered.

8. The disclosure is objected to because of the following informalities: numerous apparent spelling errors are found throughout the disclosure, for example, on page 1 line 5, page 2 line 22, and page 23 line 13.

Applicant is required to review the Application and correct the errors.

9. The use of trademarks has been noted in this application (e.g. "BIAcore" on page 18). Each letter of the trademarks should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

10. It is noted that numerous apparent spelling errors are found throughout the Claims, for example, in claim 1 ("levoratory"), claim 2 ("1wherein"), claims 4 and 5 (B71 rather than B7-1 or B7.1), claim 4 ("less" where it appears that "lower" was intended), claim 6 (period missing after claim number, and "Kd" should be denoted by subscript K_d, assuming it is intended to indicate a dissociation constant), claim 7 ("sequences ... comprises"), and others.

Applicant is required to review the claims and correct the errors.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1 – 8, 10, and 13 – 16 are rejected under **35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A) Claims 1 – 8, 10, and 13 – 16 are indefinite in the recitation of "a core motif dispersed between two flanking sequences," because it is unclear whether the claimed core motif is contiguous or interspersed with other sequences. Thus the metes and bounds of the claimed sequence are unclear, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

(B) Claim 2 is indefinite in the recitation of "flanking sequences are amphiphilic ... strands and charged amino acid residues." It is unclear whether the claimed "amino acid residues" are considered to be a subset of "sequences" or "strands." Thus the metes and bounds of the claimed sequence are unclear, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

(C) Claims 4 and 5 are indefinite in the recitation of "B7-1 ligand," because it is unclear whether the claim is directed to a ligand of B7-1 protein, such as a CD28 or CTLA-4 protein, or to a B7-1 protein itself, which is a ligand of CD28 and CTLA-4. Thus the metes and bounds of the claimed "ligand" are unclear, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

(D) Claim 4 is indefinite in the recitation of "affinity that is 10 fold greater to 2 fold less than CD28," because it is unclear whether the affinity of the mimetic for CD28, the affinity of B7-1 for CD28, or the affinity of the mimetic for B7-1 is encompassed by the claim language. Thus the metes and bounds of the claimed "peptide mimetic" are

unclear, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

(E) Claims 13 – 16 are indefinite in the recitation of a "biologically active" variant of a peptide mimetic, because the term "biologically active" is vague and indefinite, and the metes and bounds of the claimed invention are unclear. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite activity, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

(F) Claims 13 – 16 are indefinite in the recitation of a "reference" sequence, because the metes and bounds of the term are unclear. The term is not defined by the claim, the specification does not provide a standard for ascertaining which sequences are considered "reference" sequences, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention. Deleting the word "reference" from claim 13 would obviate this rejection.

(G) Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 13 – 16 are rejected under **35 U.S.C. 112, first paragraph**, because the specification, while being enabling for peptide mimetics comprising SEQ ID NOS:5 – 10, does not reasonably provide enablement for a biologically active variant of a peptide

mimetic wherein the sequences which flank the core motif are at least 70%, 80%, or 90% identical with sequences which flank the core motif in one of said sequences.

The claims recite a genus of peptide mimetics wherein the sequences which flank the core motif are at least 70%, 80%, or 90% identical with sequences which flank the core motif in one of reference sequences, but do not disclose which of the respective variants share any testable functional activity, a feature deemed essential to the instant invention. Applicant has disclosed six CD28 peptide mimetics, and thus has disclosed only six "variants". In the absence of some structural basis for the function that must be maintained by the members of the genus, the claimed invention is not described in such a way as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

Attwood (Science, 2000, Vol. 290, pp. 471-473; in particular, second paragraph) teaches that "[i]t is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences. Similarly, Skolnick et al. (Trends in Biotech. 2000, Vol. 18, pp. 34-39; in particular, page 34) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2).

Finally, even single amino acid differences can result in drastically altered functions between polypeptides. For example, Metzler et al. (Nature Structural Biol. 1997; 4:527-531) show that any of a variety of single amino acid changes can alter or abolish the ability of CTLA4 to interact with its ligands CD80 and CD86 (e.g.,

summarized in Table 2). Thus it is unpredictable if any functional activity will be shared by two polypeptides having less than 100% identity over the full length of their sequences.

In view of this unpredictability, the skilled artisan would not reasonably expect a peptide mimetic wherein the sequences which flank the core motif are at lest 70%, 80%, or 90% identical with sequences which flank the core motif in one of reference sequences, to share the same function as the peptides of SEQ ID NOS:5 – 10. The limitation of "biologically active variant" is not seen as providing a requisite guidance because there is insufficient direction as to those essential sequences for the disclosed activities.

The teachings set forth in the specification provide no more than a plan or invitation for those skilled in the art to experiment practicing the claimed invention. Thus the recitation of percent identity language does not allow the skilled artisan to make and use the claimed peptide mimetics commensurate in scope with the instant claims without undue experimentation.

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 1 – 6, 10, and 13 – 16 are rejected under **35 U.S.C. 102(b)** as being anticipated by Srinivasan et al. (1999, reference AK on IDS filed 03/24/2003; see entire document), as evidenced by the instant specification on page 14.

Srinivasan et al. teach a retro-inverso peptide analog of CD28 (page 689 paragraph 2). Srinivasan et al. teach that the end groups of the peptide can be blocked (ibid), and that the peptide binds B7-1 protein with a higher affinity than the native CD28, and inhibits proliferation and IL-2 production of $CD4^+$ T cells (page 689 paragraph 3).

The instant specification defines the retro-inverso peptide analog of CD28 as the peptide of SEQ ID NO:6.

Thus it is inherent in the teachings of Srinivasan et al. that the retro-inverso peptide analog of CD28 has the sequence set forth in SEQ ID NO:6, and has the same conformation and binding affinity as the peptide of SEQ ID NO:6.

Claims 1 – 6 are included in the rejection, because SEQ ID NO:2, the core motif of peptide mimetic claimed in claim 1, is a subset of SEQ ID NO:6.

The reference teaching thus anticipates the claimed invention.

17. Claims 1, 2, 4, 5, and 8are rejected under **35 U.S.C. 102(b)** as being anticipated by Linsley et al. (1998, US Patent 5,733,253; see entire document).

Linsley et al. teach polypeptides and fragments which bind to B7-1 protein (see entire document, e.g. Abstract). One of the polypeptides taught by Linsley et al. (SEQ ID NO:3) contains sequence which is identical to SEQ ID NOS:1 and 3 of the instant claimed invention (see the attached alignment). Linsley et al. further teach that soluble CTLA4 mutant molecules, fragments, or derivatives thereof can be used to react to B7 positive cells to regulate immune responses (see entire document, in particular, column 8 paragraphs 2 and 3). The term "fragment" is defined by Linsley et al. as a portion of the amino acid sequence of mutant CTLA4 capable of binding B7 (column 8 lines 22 – 24). Linsley et al. further provide teachings of fragments of 27 – 28 amino acids in

length containing the MYPPY sequence (SEQ ID NO:1 of the instant claimed invention), such as those which correspond to amino acids 97 – 125 of CD28 or 96 – 123 of CTLA4 (e.g. see the table at column 12). The polypeptides taught by Linsley et al. have a range of binding affinities for B7-1 (referred to as B7 by Linsley et al.) values similar to that of CD28 and lower than that of CTLA4 (see e.g. Figure 3).

Inherent in the teachings of Linsley et al. is the polyproline conformation of the polypeptides at physiological pH, as polypeptides of the same sequences will inherently assume the same conformation. The burden is on the applicant to establish a patentable distinction between the claimed and referenced polypeptides.

The reference teaching thus anticipates the claimed invention.

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

19. Claim 1 is rejected under **35 U.S.C. 103(a)** as being unpatentable over Freeman et al. (US Pat. Pub. US2002/0182727, see entire document) in view of Tezuka et al. (US Pat. Pub. US2004/0229790; see entire document).

The instant claim is directed to a CD28 peptide mimetic for blocking deleterious T cell mediated immune reaction, wherein the sequence of the core motif is MYPPPY.

Freeman et al. teach that T cell immune response can be selectively inhibited by contacting a T cell with an agent which selectively blocks the interaction of B7-2 with CD28 and/or CTLA4 (see entire document, in particular, paragraph 69). Freeman et al. further teach that such mimetic agents may be produced by synthesizing a plurality of peptides, e.g. 5 – 20 amino acids in length, and screening them for ability to bind B7-2 and thereby inhibit a B7-2 induced signal in T cells (see entire document, in particular, paragraph 71).

Freeman et al. do not teach peptide mimetic agents comprising a MYPPPY motif.

Tezuka et al. teach that the MYPPPY sequence motif is conserved in both CD28 and CTLA4, and is important for binding of these molecules to both B7-1 and B7-2 (see entire document, in particular, paragraph 12).

Thus it would have been obvious for one of ordinary skill in the art at the time the invention was made to provide mimetic agents as taught by Freeman et al. and incorporate the MYPPPY sequence motif, as taught by Tezuka et al., to disrupt binding between B7-1 and CD28, and thereby block deleterious T cell mediated immune reaction.

An ordinary artisan would be motivated to combine the teachings, because, according to teachings of Tezuka et al., regulating the interactions between costimulatory molecules, such as CD28 and B7-1, is important in the treatment of diseases (paragraph 14). Furthermore, on of ordinary skill in the art would have had a reasonable expectation of success, because Tezuka et al. teach that the MYPPPY motif is important for the interaction of CD28 with B7-1 (paragraph 12).

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

20. Conclusion: no claim is allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILIA OUSPENSKI whose telephone number is 571-272-2920. The examiner can normally be reached on Monday-Friday 9 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ILIA OUSPENSKI
Patent Examiner
Art Unit 1644

November 30, 2004

PHILLIP GAMBEL, PH.D
PRIMARY EXAMINER
TECH CENTER 1600
12/1/04